Is Buprenorphine Just a New Head for the Hydra of Opiate Addiction?

Abstract

In addition to methadone, there is another opiate replacement medication on the U.S. market, buprenorphine (as Suboxone or Subutex). While data available on buprenorphine in the U.S. suggests that it has a relatively low rate of misuse and abuse at this time, this may not continue to be the case. The International Narcotics Control Board (INCB) 2006 annual report indicated that buprenorphine is one of the psychotropic medications most frequently diverted into the illicit drug market worldwide. Anecdotal evidence indicates that despite the cautions taken for dispensing buprenorphine, many patients manipulate their physicians in order to get high from buprenorphine. There is even a website that exchanges information on how to get the most from your buprenorphine high. This paper will examine the perceived advantages and disadvantages of buprenorphine for opioid dependence treatment, assess the abuse potential of buprenorphine, and critique the supposed efficacy of maintenance treatment for opiate abuse and dependence.

Stepping Outside of the Methadone Maintenance Gauntlet[1]

The potential use of buprenorphine as an opiate maintenance treatment has been in the process of development for a number of years. The initial study demonstrating buprenorphine's effectiveness and its acceptability to patients as a treatment for opiate dependence was published in 1978. Researchers suggested that buprenorphine had potential for treating narcotic addiction since it was acceptable to addicts; that it was long-acting, produced a low level of physical dependence so that patients could be easily detoxified, was less toxic than drugs used for maintenance therapy, and blocked the effects of narcotics (Jasinski, Pevnick and Griffth 1978).

The National Institute of Drug Abuse (NIDA) supported the basic clinical research to develop buprenorphine for opioid maintenance. These scientific findings were in turn utilized by the pharmaceutical industry (Reckitt Benckiser Pharmaceuticals), and in 2002

[1] The information discussed below on buprenorphine was largely taken from "Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction," hereafter referred to as "TIP 40." It is cited in the bibliography under "Center for Substance Abuse Treatment (2004)." "TIP 40" was published online by the US Department of Health and Human Services to provide "physicians with information they can use to make practical and informed decisions about the use of buprenorphine to treat opioid addiction."

resulted in FDA approval of Subutex (buprenorphine) and Suboxone tablets (buprenorphine/naloxone) for the office-based treatment of opiate addiction by licensed physicians. Buprenorphine is believed to have less risk of abuse and dependence than Schedule II opioids such as morphine, oxycodone, fentanyl or methadone; so the FDA recommended that buprenorphine be classified as a Schedule III controlled substance, as is codeine.

The Drug Addiction Treatment Act (DATA) of 2000 allowed doctors to treat opioid dependence in their practices with Schedule III, IV or V medications in lieu of referring them to opiate treatment programs (OTPs). Until that legislation, opiate maintenance with methadone and other Schedule II substances could only be dispensed in a limited number of licensed clinics specializing in that type of treatment. The demand for maintenance treatment meant that there were not enough licensed clinics to accommodate the number of people seeking maintenance treatment. The loosening of restrictions in DATA 2000 was expected to provide patients greater access to opioid maintenance treatment.

Under the new law, Schedule III, IV and V medications used for treating opiate dependence were subject to less restrictive controls than Schedule II controlled substances, and could be prescribed by specially trained physicians. The "special training" consists of a minimum of eight hours of continuing education, which can be waived under certain circumstances. Physicians who were already certified as addiction specialists were exempt from the training requirements. The physicians also had to attest that they have the capacity to provide or refer patients for appropriate addiction counseling and other non-pharmacologic therapies; and they were limited to treating no more than 30 patients at any one time.

In December of 2006 Senator Orrin Hatch successfully attached a bill to HR 6344, an amendment to the Drug Addiction Treatment Act of 2000, which increased the number of buprenorphine patients that individual doctors may treat in their medical offices from 30 to 100. According to a cosponsor of the original Drug Addiction Treatment Act of 2000 legislation, "This common-sense fix allows many more Americans to rehabilitate their lives with bupe." A locator search of doctors (at www.suboxone.com) indicated that 99 physicians within forty miles of Pittsburgh were approved to dispense buprenorphine by September of 2008. This compares to seven licensed methadone clinics in the Pittsburgh area.

Buprenorphine Pharmacology 101[2]

Agonists, Antagonists and Partial Agonists

Full agonists bind to mu opioid receptors[3] in the brain and turn them on—produce an effect. Increasing the dose of a full agonist produces an increasing effect until a maximum

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[2]Information in the following section was taken from chapter 2, "Pharmacology," of "TIP 40."

[3]While there are different types of opioid receptors in the brain, the receptor most relevant to a discussion of opioid abuse and treatment is the *mu* receptor. It is by activating the *mu* receptor that opioids exert their

effect is reached or the receptor is fully activated. Opioids with the greatest abuse potential are full agonists. Examples of full opioid agonists include morphine, methadone, oxycodone, hydrocodone, heroin, codeine, meperidine, propoxyphene, and fentanyl.

Antagonists also bind to opioid receptors, but instead of activating them, they block the receptors from being activated by agonist compounds. Antagonists can precipitate withdrawal by displacing other opioids or blocking their effects. Examples of antagonists include naltrexone and naloxone.

Naloxone was combined with buprenorphine in Suboxone to deter people from "shooting-up" with Suboxone tablets. If an opioid-dependent individual dissolves and injects Suboxone, then the antagonistic effect of naloxone predominates over the buprenorphine because of its high bioavailability. When it's taken in this manner, the individual should experience a precipitated withdrawal syndrome (yawning, cramps and aches, pupil dilation, sweating, excessive tearfulness, runny nose, goose bumps; possible drug craving and drug seeking). Theoretically, this should decrease the likelihood of misuse and abuse of the combination tablet by the injection route. But as we will see, that's not always the case.

When naloxone (an opioid antagonist) is injected, it blocks the effects of drugs like methadone, heroin, morphine (full opioid agonists), and buprenorphine (a partial opioid agonist). When you use Suboxone under your tongue (sublingually), as prescribed, the naloxone should not inhibit the drug's effects. Sublingual naloxone has relatively low bioavailability, while sublingual buprenorphine has good bioavailability. So if a tablet containing buprenorphine plus naloxone is taken as directed—sublingually—the patient will experience a predominant buprenorphine effect. However, if you inject Suboxone, the antagonist effect of naloxone is multiplied and can result in withdrawal symptoms.

Buprenorphine is a partial opioid agonist, meaning that it possesses some of the properties of both antagonists and full agonists. It binds to receptors and activates them, but not to the same degree as full agonists like heroin and methadone. Under the right conditions, partial opioid agonists can produce effects similar to those of either agonists or antagonists. In other words, buprenorphine can potentially act like either heroin or naloxone if the conditions are right. "At lower doses and in individuals who are not dependent on opioids, full agonists (like heroin or methadone) and partial agonists (like buprenorphine) produce effects that are indistinguishable. As doses are increased, both full and partial agonists produce increasing effects." But at a certain point, the effect of a partial agonist reaches a ceiling and does not increase further. This ceiling effect seems to occur at a dosage around 16 to 32 mg. Full agonists continue to increase their effects beyond the ceiling point for buprenorphine. This ceiling applies to all of the effects mediated by mu receptors: analgesia, euphoria or respiratory depression. As higher doses are reached, partial agonists like buprenorphine can act like antagonists by occupying mu receptors but not activating them (or only partially activating them), while at the same time displacing or blocking full agonists like heroin from receptors.

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analgesic, euphoric, and addictive effects. The roles of non-*mu* receptors in the addictive process are not well defined at this time.

Affinity, Intrinsic Activity, and Dissociation

Buprenorphine has high affinity for, but low intrinsic activity at, mu receptors. The strength with which a drug binds to its receptor is termed its affinity. The degree to which a drug activates its receptors is termed its intrinsic activity. Affinity for a receptor and activation of the receptor are two different qualities of a drug. A drug can have high affinity for a receptor but not activate the receptor (e.g., an antagonist). Mu opioid agonists, partial agonists, and antagonists can vary in their affinity.

Because of buprenorphine's higher affinity for the mu receptor, full agonists cannot displace it and therefore will not exert their (the full agonists) opioid effect on receptors already occupied by buprenorphine. There will continue to be whichever opioid effect occurs from the buprenorphine. It is also difficult for opioid antagonists (e.g., naloxone) to displace buprenorphine and therefore precipitate withdrawal by occupying the receptors. Here the difference with naloxone taken sublingually or by injection comes into play. When naloxone is taken by IV, its effects are multiplied up to ten times the strength of sublingual naloxone.

Buprenorphine can also displace full opioid agonists (like morphine and methadone), which are already bonded to receptors, by blocking their effects and thus precipitate withdrawal. This effect is dose related, as shown in a study demonstrating that the 16 mg dose of the sublingual buprenorphine alone was more effective than the 8 mg dose in blocking the reinforcing effects of heroin.

In addition to variations of affinity and intrinsic activity, drugs also vary in their rate of dissociation from receptors. Dissociation is a measure of the disengagement or uncoupling of the drug from the receptor. Buprenorphine has a slow dissociation rate from the mu opioid receptor, which gives rise to its prolonged suppression of opioid withdrawal and blockade of exogenous opioids. This enables buprenorphine dosing to occur on a less frequent basis than full opioid agonists. Dissociation is not the same as affinity. A drug can have high affinity for a receptor (it is difficult to displace it from the receptor with another drug once the first drug is present), but still dissociate or uncouple from the receptor with some regularity. Buprenorphine's slow dissociation contributes to its long duration of action; it’s extended half life.

Side Effects and Abuse Potential of Buprenorphine

The most common side effects seen with both Subutex and Suboxone include drowsiness (67% chance of occurrence), nausea or dizziness (5-10% chance of occurrence), sweating headaches, vomiting (1-5% chance of occurrence). Additional adverse reactions with less than 1% chance of occurrence can include: constipation, confusion, blurred vision, weakness/fatigue, dry mouth, nervousness, depression, and slurred speech. Many of the symptoms are similar to those evident with other opioids such as heroin and oxycodone. These effects usually peak in the beginning of treatment with Subutex or Suboxone, but may last a number a weeks. Clinical data indicate that the risk of serious diminished breathing may be less with buprenorphine than other opioids when used in high doses or in overdose situations. Nonetheless, buprenorphine has been

associated with deaths due to diminished breathing, especially when used in combination with alcohol or other Central Nervous System (CNS) depressant drugs.

Although the abuse potential is reportedly lower for buprenorphine than full opioid agonists like heroin and morphine (because of the ceiling and partial agonist effects), several studies indicate that it can be abused (See "Tip 40" for several citations). This abuse potential is to be expected with all forms of buprenorphine because of its action at the mu receptor. However, the potential is allegedly lower in comparison with full agonists like heroin and oxycodone, given buprenorphine's partial agonist effects and the resultant ceiling in maximal effects produced. Even though buprenorphine can precipitate withdrawal under certain circumstances, it is worth noting that it does not usually produce severe precipitated withdrawal symptoms.[4]

A study by Strain, Stoller, Walsh and Bigelow (2000) found that "sublingual buprenorphine and buprenorphine/naloxone may both be abused by opioid users who are not physically dependent upon opioids." "Tip 40" discussion of the Strain et al. research additionally noted that the onset of effects via the sublingual route is slower than that if buprenorphine is injected or snorted, suggesting that the abuse potential is higher if buprenorphine is injected or snorted. The naloxone should precipitate some withdrawal symptoms and theoretically discourage this abuse, but that is not always the case.

The abuse potential of buprenorphine in individuals who were physically dependent on opioids varied as a function of three factors: (1) the level of physical dependence, (2) the time interval between administration of the full agonist and of buprenorphine, and (3) the dose of buprenorphine administered.

Level of Physical Dependence. In individuals with a high level of physical dependence (e.g., those using substantial amounts of opioids on a daily basis), buprenorphine could precipitate withdrawal when taken during the time of opioid intoxication or receptor occupancy.

Time Interval. The abuse potential of buprenorphine in opioid dependent individuals also varies as a function of the time interval between the dose of agonist and the dose of buprenorphine. At relatively short time intervals (e.g., 2 hours after a dose of methadone), buprenorphine can precipitate withdrawal—even when the level of physical dependence is relatively low. At longer time intervals, it becomes more likely that buprenorphine will exhibit either no effects (i.e., similar to placebo) or effects similar to opioid agonists (euphoria).

Dose of Buprenorphine. Finally, the dose of buprenorphine administered also can influence its abuse potential. Low doses of injected buprenorphine (e.g., ≤2 mg) produce minimal effects in opioid dependent patients and are primarily identified as similar to placebo; although there has been at least one report of more precipitated abstinence. Higher doses can be agonist-like, especially as the time interval since the dose of agonist

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[4] Discussion in "TIP 40" seems to minimize the abuse potential of buprenorphine by noting reports of abuse for only its analgesic (liquid) form or diverted Subutex, with no direct mention of potential abuse of Suboxone. See the section below, "Listening to the Opiophile," for specific anecdotal information on how Suboxone can be abused.

increases (e.g., 24 or more hours) and if the individual has a lower level of physical dependence (e.g., 30 mg per day of methadone or the equivalent).

Looking at the Research

Office-Based Buprenorphine Treatment in the U.S.

Several of the published studies reviewed here agreed with Rosack (2003) that buprenorphine was "safe and effective at reducing opiate use and craving when administered in an office-based setting." Fudala et al. (2003) said that both Subutex and Suboxone were safe; and able to reduce the use of and craving for opiates. 55.3% of the participants received at least six months of Suboxone treatment. Stein, Cioe and Friedmann (2005) reported that 59% of the patients enrolled in the study remained in treatment for six months. Mintzer et al. (2007) found that 54% of the patients treated in primary care facilities with limited resources for addiction treatment were 'sober' at six months, a designation that I found problematic because of the vague and subjective way the authors seem to have used the term. It was not clear if the sobriety of the participants at six months meant they were abstinent from all drugs or just opioids.

Another study by Moore et al. (2007) suggested that the type of opioid abused was an important factor in office-based buprenorphine/naloxone treatment. They found that individuals dependent upon prescription opioids were more likely than heroin-only patients to complete treatment (59% versus 30%), to remain in treatment longer (21 versus 14.2 weeks), and to have a higher percentage of opioid-negative urine samples (56.3% versus 39.8%). The significance of these studies (Fudala, Stein, Mintzer and Moore) for our purposes are that they were all conducted within the U.S.; and that the effectiveness of these studies was primarily based upon their retention success.

Summary of the Reviewed U.S. Studies

Generally there was a retention rate between 54% and 59% percent over six months of office-based buprenorphine treatment within the above noted studies, which was considered to be a positive 'treatment' result. Consider that this simply means that the participants were still reporting to receive their Suboxone 'treatment' after six months. Even then, 46% to 41% of the original participants had dropped out, seemingly because of continued opiate use.

Concurrent drug use was a concern for many participants of the studies, even after six months of Suboxone treatment. Studies that reported data on positive opioid urines during the course of treatment (Fiellin/Moore and Fudala) noted between 32 and 64 percent of those who remained in buprenorphine treatment used opiates during the course of their treatment. About 40% of those still in treatment after six months used cocaine at some point; positive reports ranged between 24.5% and 53.5%.

Benzodiazepine use was only reported in Fudala; and was relatively low at 10%. This is misleading, because several of the studies reviewed here excluded participants who reported previous abuse of benzodiazepines or alcohol. While this exclusion is consistent with the contraindications noted by TIP 40 for office-based buprenorphine treatment, opioid dependent individuals regularly abuse benzodiazepines with maintenance drugs

like methadone and buprenorphine because of the heroin-like high of the combined effect. Anecdotal information reviewed later suggests that benzodiazepine use among office-based buprenorphine treatment is probably much higher than that reported by Fudala et al.

Lintzeris, Mitchell, Bond, Nestor and Strang (2007) noted that about 33% of methadone maintenance patients reported using benzodiazepines in any given month. The researchers also noted that high dose (40mg) diazepam was associated with time-dependent (1 to 3 hours from use) increases in the intensity of subjective drug effects with methadone and buprenorphine. The Lintzeris et al. study further reported that benzodiazepines were present in 40–80% of the opiod-related deaths reviewed for the study. Concurrent benzodiazepine abuse is therefore a major concern with buprenorphine maintenance treatment.

A Closer Look at Kakko et al.

A Swedish study by Kakko, Svanberg, Kreek and Hellig (2003), published in the British journal *Lancet*, described an even more dramatic outcome with office-based buprenorphine treatment than the above noted U.S. studies: 75% of the participants were still in active after one year, while all but one member of the placebo group had dropped out before 50 days of treatment. The final placebo patient dropped out near 60 days of treatment. In every case, the reason for the drop outs was because urinalysis showed participant drug use. Because of its dramatic outcome differences, we will take a closer look at the Kakko study.

Kakko et al. (2003) noted that "Abstinence-oriented treatment continues to be the most commonly offered treatment option in Scandinavia and many other parts of the world, however, this approach is not supported by evidence." (p. 662) Without parallel treatment with maintenance drugs such as methadone, the authors suggested that psychosocial interventions have consistently failed to demonstrate effectiveness because of the low retention rates despite long detoxification periods and intensive psychosocial interventions. Effectiveness for the Kakko et al. study was then based upon an assessment of the retention rate in treatment, as were the studies reviewed above. But an examination of the Kakko study's methodology suggested several factors that may have contributed to the dramatically different retention rates.

While placebo patients were given access to buprenorphine during the first six days of treatment to provide treatment for opiate withdrawal, the regimen was halved every two days (8mg, 4 mg and 2mg), while the buprenorphine-assisted participants who began with an initial dose of 8mg of buprenorphine had their dose doubled on the second day, where it remained throughout the study. The relatively short period of medically supervised withdrawal for placebo patients in the study has been shown to be less effective than moderate (between 3 and 30 days) or long term (over 30 days) regimens for withdrawal. Brief withdrawal periods do not produce measurable long term benefits; and patients usually relapse to opioid use—as was found by Kakko et al. See chapter 2 of TIP 40 for more information on medically supervised withdrawal with buprenorphine.

The Kakko et al. study indicated that 18 of the eventual drop outs from the placebo group occurred (roughly) within the first three weeks of treatment. This was despite the

availability of intensive psychosocial support and relapse prevention treatment. At least two possible factors could have precipitated the rapid initial dropout rates. First, even though the prescribed relapse prevention treatment began within the first four weeks of the treatment study, the placebo group dropouts did not stay in treatment long enough to learn and apply the relapse prevention strategies. They resumed active drug use and dropped out of treatment before the strategies could be effectively learned or implemented.

Second, the short term withdrawal protocol for the placebo group meant that its members were more likely to struggle with cravings and other post acute withdrawal symptoms that typically occur in the first weeks of opiate abstinence. A so-called "withdrawal phobia" has long been postulated as one of the major obstacles for opiate addicts to overcome in order to establish abstinence from opiates. This seems to include both acute physiological withdrawal and the ongoing struggle to feel "normal" that characterizes the post acute withdrawal syndrome. Placebo group members would be more likely to have post acute withdrawal symptoms and want to self-medicate these symptoms. The placebo group was also be more likely to lapse into active drug use versus re-engaging in the treatment process after an initial one time use, since they would be concerned about experiencing acute withdrawal.

It could further be expected that time seeking heroin (and failure to report to the clinic), as well as a more rapid accumulation of positive urines, meant that placebo group members saw they had little chance of remaining in the study and simply stopped trying. By contrast, the first dropout from the buprenorphine-assisted group for drug use didn't occur until well after one hundred days of the study.

The authors did acknowledge that the high attrition rate was partly due to the study's criterion that participants who continued to use illicit drugs would be involuntarily discharged from treatment. The study's protocol required that more than two positive urines within three months for any banned substance would result in discharge from the study unless the patient agreed to and complied with intensified support efforts. But they then noted that as this discharge criterion was similar to that in other agonist assisted programs (i.e. methadone maintenance), that it was "a realistic design feature to assess clinical efficacy." So, buprenorphine was shown to be more effective in retaining opiate addicts in maintenance treatment than a placebo, even with the availability of intensive psychosocial support and relapse prevention training. This is hardly a surprising result to clinicians who work regularly with opiate addicts and see their withdrawal phobia in action. Among many opiate addicts, anything goes in order to avoid or minimize withdrawal; even resumption of the heroin they want to abstain from.

The authors did note that it was important to consider whether withdrawal symptoms in the placebo group contributed to dropout from the study. However, they said the initial dose regimen in the placebo group was identical to that used throughout Sweden for treating heroin withdrawal "and seems satisfactory in those settings." This may be true for acute withdrawal symptoms, buprenorphine-assisted and placebo participants alike, but it would not apply for post acute withdrawal symptoms. Placebo group participants in the study would have been expected to experience more intense post acute withdrawal and

lapse into active opiate use earlier and more frequently than buprenorphine-assisted participants.

In any event, it is clear that with multiple lapses back into active drug use within the first three weeks of the study, patients within the placebo group could clearly see that the study was not effectively helping them establish abstinence from heroin and apparently did not see the benefits of the intensive psychosocial support as worth remaining in the study.

Another factor influencing the positive results of the study was the daily monitored ingestion of buprenorphine for at least six months, which helped to behaviorally shape the desired protocol for buprenorphine maintenance. The only option for patients was to ingest their buprenorphine or placebo as prescribed. They couldn't skip doses and hoard their medication; or crush pills in order to snort or inject them. Supervised ingestion was effective in ensuring that the buprenorphine was taken as prescribed. In most office-based treatment settings, patients are only observed ingesting buprenorphine for the first few doses, and then left to take their daily at their leisure.

Co-occurring drug abuse was an additional concern with some of the participants of the Kakko et al. study. Urine screens among the patients remaining in treatment were 25% positive for illicit opiates, central stimulants, cannabinoids and benzodiazepines. While this is lower than other studies we reviewed, it still indicates the persistence of a desire to "get high" in some opiate dependent individuals, even when their acute withdrawal symptoms are effectively minimized by buprenorphine.

The results reported by the study don't appear to be that dramatic after a closer look. The treatment methodology encouraged an early dropout rate for the placebo group, thus enhancing the outcome noted for the buprenorphine-assisted group. The study also failed to acknowledge or control for the pervasive influence of post acute withdrawal symptoms on the treatment retention of placebo group members. Additional control groups with a more gradual withdrawal protocol than the short term (six day) withdrawal used within the placebo group needs to occur in future research studies attempting to build upon the results reported here. Given some of the medical concerns with the wider use of methadone as a maintenance drug, and fears that it could become a primary drug of abuse with increased methadone diversion into uncontrolled street use, the authors suggested that buprenorphine might be "a useful complementary or alternative option to methadone." (p. 662) However it does not appear to be as "highly efficacious" as its authors claimed; unless remaining in long term buprenorphine-assisted maintenance treatment, perhaps for life, is considered to be desirable.

While the above cited research gives the appearance of being an impressive step forward in the treatment of opioid addiction, it also masks a trend away from abstinence-based treatment of opioid dependence. The goal is to develop and maintain a dependence on buprenorphine in order to treat individuals with a dependence on heroin or other opiates. The goal is to treat opioid dependency by developing a dependency to another opioid. This "treatment" is corrective, not curative. Staying in treatment to remain on buprenorphine maintenance and making concurrent improvements in quality of life measurements like the addiction severity index (ASI) is now the goal of treatment, not eventual abstinence. Establishing and maintaining abstinence is increasingly considered to be an unrealistic and ineffective treatment strategy for opiate addicts. But is this corrective

treatment ultimately beneficial or the introduction of a slow growth, progressively addictive tumor?

Diversion and Burprnorphine Abuse

The International Narcotics Control Board (INCB) 2007 annual report was concerned with buprenorphine abuse and diversion, noting that it occurred mainly in Europe, where buprenorphine has been used for treating opioid addiction since the 1990s. "The increasing prescription of opioids, such as buprenorphine and methadone, for substitution treatment also contributes to the problem of polydrug abuse, as well as the problem of diversion." Because of the diversion problem, the INCB requested that all countries reporting legitimate use of buprenorphine also provide information on the control status of buprenorphine:

> The Board calls on the competent authorities of all countries concerned to increase their vigilance with regard to the diversion and abuse of and trafficking in buprenorphine and to inform the Board of new developments. The Board encourages all Governments concerned to consider enhancing existing mechanisms for control over that substance, as necessary. (INCB 2007, 23)

This diversion often involves theft from factories and wholesalers; falsified prescriptions; and the dispensing of preparations by pharmacies without the required prescriptions. Large-scale diversion of buprenorphine from domestic distribution channels in India has led to local abuse problems and smuggling. "Bupe" has become the main IV drug of choice in most areas of India. Authorities of the United Arab Emirates reported seizing of 28,800 ampoules of buprenorphine (Buprenex) which was smuggled out of India in 2005. Authorities in Pakistan (February 2006) seized 29,883 ampoules of Buprenex originating in India and allegedly smuggled into Pakistan out of Afghanistan. Smuggling of buprenorphine from India into its neighboring countries (Bangladesh, Bhutan, Nepal and Sri Lanka) remained a major concern in 2007. The Islamic Republic of Iran is another favorite destination for buprenorphine smugglers (INCB 2006). The island country of Mauritis (550 mile east of Madagasgar in the Indian Ocean) reported a recent seizure of 50,000 tablets of Subutex reportedly originating in France (INCB 2007)

Several European countries have abuse and diversion problems with buprenorphine as well. In France, where buprenorphine is widely used in treating heroin addicts, as it is in the U.S., it is estimated that 20-25 per cent of the tablet form of buprenorphine (Subutex) may be diverted to the illicit market. Nearly half of the clients who used buprenorphine reported injecting their own buprenorphine (Vidal-Trecan, Varescon, Nabet and Bolssonnas 2003) and 79% of needle and syringe program clients who used buprenorphine reported injecting it within a month of the survey (Vanelciano Emmanuelli and Lert 2001). In 1993, buprenorphine was identified as the most commonly abused drug by IV drug users in Scotland, which then led to it being withdrawn from the market. Six years after buprenorphine was introduced as an analgesic in Ireland, a study of opiate users presenting for help at one treatment center found the proportion who reported buprenorphine abuse rose from 0 to 80% in a twelve month period. In Spain, one study

indicated that 71% of opioid-dependent clients reported some use of buprenorphine, usually by injection.[5]

Subutex has also been found on the illicit market in the Czech Republic and Finland. The buprenorphine preparations available on the illicit market in Finland seem to have been smuggled into that country. According to recent information provided to the Board by the Belgian authorities, Subutex tablets destined for Georgia were seized in Belgium. Significant increases in both the quantity and the number of seizures of buprenorphine have also been reported in Mauritius; the authorities of that country reported that, as buprenorphine can be smuggled more easily than heroin or cannabis and there was a shortage of heroin during 2005, drug traffickers and abusers have been increasingly turning to buprenorphine (INCB 2006).

Since the year 2000, the number of countries importing buprenorphine has more than doubled. The total manufacture of the substance increased steadily from 1993 onwards, reaching an average of nearly 2 tons between 2003 and 2006; double the amount manufactured in the late 1990s, when buprenorphine started to be used in higher doses for the treatment of opioid addiction (INCB 2007).

The U.S. has yet to experience such diversion and abuse problems with buprenorphine, probably because of the relative newness of its availability in this country. Cicero and Inciardi (2005) reported on data gathered from structured interviews of suspected drug abusers and found that buprenorphine abuse was "no greater than that observed for the unscheduled drug tramadol and much less than that for the Schedule II drugs methadone and oxycodone." They concluded that the fears of the FDA and DEA about a surge in buprenorphine abuse as a result of its use in opioid-dependent maintenance may be unfounded, at least through the first two years of its availability. But in the following section, "Listening to the Opiophile" we examine evidence for a growing sub culture of buprenorphine abusers among the larger population of opiate abusers.

Fatalities With Buprenorphine

A British study (Schifano et al. 2005) examined data on buprenorphine mortality between 1980 and 2002. They concluded that "In combination with other drugs, buprenorphine lethality risk is probably increased." (Schifano et al. 2005, 345) Buprenorphine was frequently taken in conjunction with opiates and painkillers by the fatalities studied in the Schifano study. Schifano also reported that while the blood levels of 117 fatalities for buprenorphine were mostly within the therapeutic range, "a concomitant intake of benzodiazepines" acted as a major risk factor for such fatalities. Although it is not known definitely if this is a pharmacodynamic interaction, the researchers suggest it is, since both buprenorphine and benzodiazepines are CYP3A substrates. In seven mortality cases, buprenorphine alone was detected, raising questions about the reported high safety profile suggested in the studies reviewed here and elsewhere.

The Schifano study underscores the importance for physicians to be cautious when prescribing buprenorphine to individuals in conjunction with benzodiazepines, as well as

[5] These findings were originally reported in Jenkinson et al. (2005).

in prescribing buprenorphine to patients who are suffering from chronic pain or who demonstrate a likelihood of concurrent opiate use while taking buprenorphine. Overdose and death are potential outcomes when buprenorphine is combined with other CNS depressants.

Buprenorphine has been available in France as an outpatient treatment for opioid dependence since 1996. Since that date, several deaths have been attributed to the drug. Post mortem blood samples in one study even indicated that buprenorphine and its primary metabolite appeared to be within the therapeutic range. Intravenous injection of crushed tablets, a concomitant intake of psychotropics (especially benzodiazepines and neuroleptics) and the high dosage of the buprenorphine formulation available in France appear as the major risk factors for such fatalities. Only two of the deaths appeared to be suicide-related (Kintz 2001).

Rehabilitating or Ravaging Lives?

The intractableness of opioid withdrawal has long been recognized as a major reason for opiate addicts to resume active drug use, even when they have a strong desire to abstain. This so-called "withdrawal phobia" has long been postulated as one of the major obstacles for opiate addicts to overcome in order to establish abstinence from opiates. This phobia includes both acute physiological withdrawal and the ongoing struggle to feel "normal" that characterizes the post acute withdrawal syndrome. So delay or disruption of the withdrawal process has been traditionally one of the goals of opioid maintenance therapies.

As with methadone, buprenorphine has a longer half-life than other opiates.[6] The longer half-life delays the onset of withdrawal, a characteristic which is considered an asset for maintenance therapy drugs such as methadone and buprenorphine. Patients don't have to take methadone or buprenorphine as frequently as other opioids to stop withdrawal; which then theoretically minimizes the abuse potential of both drugs because of the delayed onset of withdrawal and the ready availability of methadone or buprenorphine. Patients also don't obsess about taking something to stop or prevent withdrawal; and they decrease negative behaviors (interpersonal, social and legal) to obtain something to prevent withdrawal.

There is not a very long history of buprenorphine maintenance in the U.S., but the even longer half-life for buprenorphine suggests that similar problems to those noted with methadone maintenance will occur in time. Especially with attempted withdrawal from long term buprenorphine maintenance, expect that the extended half life for buprenorphine will mean an even longer post acute withdrawal phase for buprenorphine dependent individuals than with methadone. Even if this is less intense than the post acute withdrawal experienced by heroin addicts, the prolonged time of not feeling "normal" may place buprenorphine maintenance clients at a greater risk of lapsing into active opiate use.

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[6]Full agonist opioids such as morphine, heroin, Codeine, Demerol and Dilaudid have half-lives between 2 and 4 hours; methadone has a half-life of around 22 to 25 hours; buprenorphine has a mean half-life of approximately 37 hours (ranging between 20 and 73 hours).

In fact, with methadone, it seems that most patients relapse to active opiate use or resume methadone maintenance even after they have successfully tapered off of methadone (Magura and Rosenblum 2001). It seems that something similar to this expectation may be a factor in ongoing buprenorphine maintenance being recommended over any form of tapering or withdrawal. Maintenance treatment for opioid dependence becomes a life long process.

But is this "treatment" or social control? Long term, daily buprenorphine use essentially ensures physical dependency; and creates a pool of "patients" who face potential lifelong maintenance treatment. Instead of being at the mercy of drug dealers, buprenorphine patients are at the mercy of the medical personnel who dispense it. Additionally, the buprenorphine dependent patient who seeks to withdraw from Suboxone and become abstinent has to walk through a gauntlet of his or her own making: a daily buprenorphine intake for the entire time they were taking Suboxone or Subutex. How many opioid addicts are successful enough in their active addiction to procure their drug of choice regularly enough to avoid withdrawal symptoms for months or years at a time? The longer a behavior is reinforced, the harder it is to extinguish regardless of whether or not it has a ceiling effect to its withdrawal symptoms or not. The pharmacological evidence clearly indicates that repeated administration of buprenorphine (as with outpatient maintenance therapy) produces or maintains physical dependence on opioids.

A disturbing aspect of the clinical guidelines for buprenorphine treatment in "TIP 40" is a self-conscious exploitation of the euphoric effects of buprenorphine to encourage treatment compliance. Within a section entitled "Consequences of Repeated Administration and Withdrawal of Opioids" Tip 40 noted that tolerance was a decreased subjective and objective response to the same amount of opioids over time, leading to increasing the amount used to achieve the desired effect. "In the case of abuse or addiction, the desired effect typically is euphoria." Amazingly, in another sections the publication also identified the presence of this subjective effect positively, because it encourages patient compliance with buprenorphine treatment:

> These subjective effects aid in maintaining compliance with buprenorphine dosing in patients who are addicted to opioids. . . . Buprenorphine's partial mu agonist properties make it mildly reinforcing, thus encouraging patient compliance with regular administration. ("TIP 40." Chapter 2, Pharmacology)

One of the "benefits" of buprenorphine therapy is the patient gets a euphoric "high" feeling that motivates them to continue taking buprenorphine. Does this sound familiar? Think here about the "benefits" of drinking . . . or (put the drug of your choice here).

Listening to the Opiophile

There is a growing amount of anecdotal evidence that office-based buprenorphine maintenance may actually be promoting dependency within addicts who are not truly ready to stop abusing opiates. Opiate addicts seeking buprenorphine quickly learn what doctors look for to assess their appropriateness for office-based buprenorphine treatment

and what excludes them. It's as easy as doing a Google search for buprenorphine or networking with other addicts. They can quickly decide on which doctors to try next if one doctor determines that they are not appropriate for office-based treatment; again by a Google search for buprenorphine treatment or by talking with other opiate addicts. And they will have learned what not to say to the second doctor. Doctor shopping and addicts sharing information on which doctors to see and how to get what you want from doctors are the tried and true methods of prescription drug abuse, which is now roughly equal to that of illicit drugs in the US. "The number of Americans who abuse prescription drugs nearly doubled from 7.8 million to 15.1 million from 1992 to 2003."

What follows are excerpts from the website opiophile.org, established in 2004 "as a sounding board for the exchange of ideas in everything opiate. This includes the history of, chemistry of, experience with, or any other aspect of opiate-related information." The opiophile site gets a fair amount of internet traffic, according to the website "quantcast" (http://www.quantcast.com/opiophile.org), which estimated that Opiophile receives 36,537 visits per month. 10,806 of these are unique visitors, who average 3.38 visits per month. The postings are given without editing; not all the postings under each discussion thread are used here. Go to the site and read at your leisure.

Under a buprenorphine discussion thread titled "how I enjoy my sub," was the following post and responses:

"the only time i actually get that sorta doped out feeling is when i take subs, a few mg of klonopin, a half (or less) .1 pill of clonodine and a few ambians. anyone else with any other sort of safe cocktails they enjoy>?"

"I do not take suboxone anymore. But to achieve a nod or at least good effects you need to take 2-4mg suboxone and then benzos. It is a great synergy that works."

Under another thread entitled "Sub's and Benzo's:"

I will see what I can weasle out of my doctor tonight and play it by year maybe if I am super super lucky the peice of shit will send me home with a script for .25mg xanax... hahaha.

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agreed, its bullshit, everyone i know who gets suboxone (including me) also gets scripted benzo's even the strong ones like k-pins xanax and halcion. however i have met doctors who believe benzo's to be extremely addictive, moreso than opiates and therefore will not prescribe them to ppl with history of addiction.

Under the thread "The Ultimate Sub Guide."

Most doctors will prescribe suboxone by default, and some are apprehensive to prescribe subutex (because of it's higher abuse potential). If you wish to take subutex instead of suboxone, during your first appointment you can ask your doctor for it. If he declines, just accept your first suboxone script, then on your next visit, complain of headaches (it's one of the most common side effects of suboxone, and is associated with the nalaxone), and s/he should switch you over to subutex. Of course, there is going to be some doctors out there who just won't prescribe subutex.

Buprenorphine myths:

The nalaxone in suboxone will cause you to go into withdrawls if you take them in a way other than sublingually (like IV or insuffulation).

Nalaxone was added into suboxone for precisely the reason of preventing abuse through alternative ways of administration, but many people have found that it doesn't actually work for this. Many people, including those on this forum, routinely IV or insuffulate their sub doses, although subutex is much better for this (not only because it's lacking the nalaxone, but because it's also lacking the dyes and flavoring that suboxone has).

Here is a posting from an older thread from 11-10-2005, "Crushing suboxone."

been on suboxe for 3 years. and I just started snorting it. Yes it does work, but you have to manipulate it and you can't be on more then 4-8mg/day. Just snort twice as much as you are prescribed to take orally and you definitely feel high. Its a LOT of powder, but I do it a few times a month with my prescription. You can manipulate it by taking it orally too. I was being prescibed 8 mg/day (30 pills), but brought myself down to actually only use 2-4mg/day. That gave me a bunch of pills to expereiment with each month. I will take 2-4 mg/day for 1-2 weeks then take 16mg one day, and its just a nice little occasional buzz that keeps my obsessive mind away from street drugs. never shot it though--heard too many "ended up in the emergency room" stories. But if snorting suboxone doesn't send u into w/d's why would shooting it? not willing to go there though.

The Hydra-Headed Monster of Opiate Addiction and Treatment[7]

Historically, technological and medical advances with opiates have repeatedly introduced a further extension of the abuse potential with opioids. Morphine was first isolated from opium in 1802 by a German pharmacist. The development of the hypodermic syringe in the mid-nineteenth century (1855) by Dr. Alexander Wood and Charles Gabriel Pravez allowed the injection of pure morphine. The first recorded fatality from a hypodermic-syringe induced overdose was Dr Wood's wife, because she was injecting morphine to excess.

By the late nineteenth-century in America, opiates were cheap, legal and abundant. In the words of one historian, America had become "a dope fiend's paradise." Ironically, it was believed that if morphine was injected, it wasn't addictive. Quitting habitual opium use was known to cause discomfort, flu-like symptoms, and depression; so morphine seemed an excellent cure. In China, for instance, early twentieth century missionaries handed out anti-opium remedies in such profusion that the pills became known as "Jesus Opium." Their active ingredient was morphine.

Dr. John Witherspoon, later the President of the American Medical Association, in addressing this growing problem, exhorted the medical community to "...save our people from the clutches of this hydra-headed monster which stalks abroad through the civilized world, wrecking lives and happy homes, filling our jails and lunatic asylums . . . "

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[7] Information in this section was taken from the following sources cited in the bibliography: Methadone 2. (nd). "A History of Methadone," Opioids.com (nd)a. "A Brief History of Opium," Opioids.com (nd)b. "Hidden Pain in a Pill."

(opioids.com n.d.c) So the search began for a powerful non-addictive alternative to opium and morphine.

In 1874, an English pharmacist boiled morphine and acetic acid to produce diacetylmorphine. Diacetylmorphine was synthesized and marketed commercially by the German pharmaceutical company, Bayer. In 1898, Bayer launched the best-selling drug–brand of all time, Heroin. The company handed out free samples to physicians and sold it in dozens of countries as "the sedative for coughs." The medical profession was largely unaware of the potential risk of heroin addiction for several years. A philanthropic organization in the U.S., the Saint James Society, mounted a campaign to supply free samples of heroin through the mail to morphine addicts who are trying give up their habits. Eventually, doctors noticed that some of their patients were consuming large quantities of heroin–based cough remedies. It appeared that heroin was not the miracle–cure for morphine addiction that some of its early boosters had supposed. In 1913, Bayer halted production.

Methadone was first synthesized by German chemists in the late 1930s, but was not brought into commercial production during the war. After the war, the factory where methadone was invented fell under American control; and the U.S. began the first clinical trials of methadone in 1947. At first doctors believed methadone would be a revolutionary new painkiller, but by the early 1950s it was hardly being used at all. Then in 1964, Drs Marie Nyswander and Vincent Dole in New York were looking for drugs to help heroin users, when they read about methadone in the medical literature. They found it helped their patients stop using heroin; and that tolerance to methadone was slow to develop—and so methadone maintenance treatment was born.

There is a dramatic lifestyle change in the initial stages of MMT for many people. Testimonies and research suggesting that methadone is a wonder drug that saves lives abound. Stability and the resumption of an almost normal life are possible. Ironically, Magura and Rosenblum (2001), the authors of an analysis of post discharge outcomes from methadone maintenance programs, pointed out that the number of "long term" stable patients (5 years or more of MMT) has never been very large. In fact, nationally, one half of all admissions to MMT leave within one year.

Magura and Rosenblum (2001) further noted that "Virtually all of these studies document high rates of relapse to opioid use after methadone treatment is discontinued." While most patients left treatment without meeting the established criteria for detoxification from methadone, high relapse rates were also reported for patients who completed their respective programs. Focusing on the high social costs from illegal opiate addiction, and the high rate of relapse to active opiate use among MMT patients attempting to taper off of methadone, the authors recommend a "harm reduction" treatment model of long term and even lifelong opiate replacement. Patients should not be "pressured" to accept abstinence by touting its "supposed desirability or superiority." In other words, find ways to keep them in ongoing opiate replacement treatment without feeling pressured by therapy staff to accept abstinence as a treatment goal. In fact, you should probably discourage patients from setting an abstinence-based treatment goal for an indefinite period of time. Another study reviewing the historical and clinical issues associated with methadone maintenance suggested: "It may be necessary for patients to remain in

treatment for indefinite periods of time, possibly for the duration of their lives." (Joseph, Stancliff and Langrod 2000, p. 361)

Conclusion and Summary

Into the above social and political context buprenorphine was approved by the FDA for the maintenance treatment of opioid addicts in 2002. It doesn't require the same limitations or problems as methadone maintenance; it's newer and better: "an effective treatment for heroin dependence' (Fiellin et al. 2002); "a safer medication" than those traditionally used for the treatment of opioid dependence (McCance-Katz 2004); "a useful complement to methadone maintenance treatment" (Kakko et al. 2003); "The public health benefits appear to far outweigh the risk to individuals or to the community" (Fiellen et al. 2004a); the results suggest that "new types" of patients are entering treatment (Sullivan et al. 2005); it provides a new medical paradigm and "the opportunity to dramatically increase access to the most effective treatment for opioid dependence" (Fiellen et al. 2004b).

The above historical review suggests that the "hydra-headed monster" of opiate addiction will not be vanquished by any new and (supposedly) better opioid derivative. Historically, the "new and better" compounds were eventually turned into monsters in their own right. Technological advances were co–opted to serve the advancement of opioid addiction or easily overcome. If the experience with methadone and other opioids is any indication, we can expect to see the problems noted above to occur with buprenorphine. However, it may take some time before we have accurate data; and thousands of opioid dependent individuals will have added buprenorphine to their list of used and abused substances. There will be a new head for their hydra.

Bibliography and Works Cited

Center for Substance Abuse Treatment. (2004)."Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction." *Treatment Improvement Protocol* (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. [online]. Available: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat5.chapter.72248

Cicero, T.J. and Inciardi, J.A. (2005). "Potential for abuse of buprenorphine in office-based treatment of opioid dependence." *New England Journal of Medicine,* 353 (17), 1863-65.

FDA Talk Paper. (2002). "Subtex and Suboxone Approved to Treat Opiate Dependence." T02-38 [online]. Available: http://www.fda.gov/bbs/topics/ANSWERS/2002/ANS01165.html

Fiellin D.A., Pantaloon M.V., Pakes J.P., O'Connor P.G., Chawarski M. and Schottenfeld R.S. (2002). "Treatment of heroin dependence with buprenorphine in primary care." *American Journal of Drug and Alcohol Abuse,* 28, 231-241.

Fiellin D.A., Kleber, H., Trumble-Hejduk J.G., McLellan A.T. and Kosten T.R. (2004a). "Consensus statement on office-based treatment of opioid dependence using buprenorphine. *Journal of Substance Abuse Treatment,* 27, 153-159.

Fiellin D.A., O'Connor P.G., Chawarski M. and Schottenfeld R.S. (2004b). "Processes of care during a randomized trial of office-based treatment of opioid dependence in primary care." *The American Journal on Addiction,* 13, 567-578.

Fiellin DA, Pantalon MV, Chawarski MC, Moore BA, Sullivan LE, O'Connor P.G., Schottenfeld RS. (2006). "Counseling plus buprenorphine–naloxone maintenance therapy for opioid dependence." *New England Journal of Medicine,* 355, (4), 365-374. [online]. Available: http://content.nejm.org/cgi/reprint/355/4/365.pdf

Fudala P.J., Bridge T.P., Herbert S., Williford W.O., Chiang C.N., Jones K., Collins J., Raisch D., Casadonte P. and Goldsmith R.J. Buprenorphine/Naloxone Collaborative Study Group. (2003). "Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone." *New England Journal of Medicine,* 349, (10), 949-958. [online]. Available: http://content.nejm.org/cgi/content/full/349/10/949

International Narcotics Control Board. 2006. "Report of the International Narcotics Control Board for 2006." [online]. Available: http://www.incb.org/incb/index.html

International Narcotics Control Board. 2007. "Report of the International Narcotics Control Board for 2007." [online]. Available: http://www.incb.org/incb/index.html

Jasinski D.R., Pevnick J.S. and Griffth J.D. (1978). "Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction." Archives of General Psychiatry, 35, (4), 501-516.

Jenkinson R.A., Clark N.C., Fry C.L. and Dobbin, M. (2005). "Buprenorphine diversion and injection in Melbourne, Australia: an emerging issues?" *Addiction,* 100, 197-205.

Join Together. (2007). "New Law Expands Access to Buprenorphine." [online]. Available: http://www.jointogether.org/news/features/2007/new-law-expands-access-to.html

Joseph H., Stancliff S. and Langrod J. (2000). "Methadone maintenance treatment (MMT): A review of historical and clinical issues." *Mount Sinai Journal of Medicine,* 67, (5-6), 347-364.

Kakko, J., Svanborg, K.D., Kreek, M. J., Hellig, M. (2003). "1 year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden." *Lancet*, 361, 662-668.

Kintz, P. (2001). "Deaths involving buprenorphine: a compendium of French cases." *Forensic Science International,* 121, (1-2), 65-69.

_____. (2002). "A new series of 13 buprenorphine-related deaths." *Clinical Biochemistry,* 35, (7), 513-516.

Lintzeris, N., Mitchell, T., Bond, A., Nestor, L. and Strang, J. (2007). "Pharmacodynamics of diazepam co-administered with methadone or buprenorphine under high dose condition in opioid dependent patients." *Drug and Alcohol Dependence,* 91, 187-194.

McCance-Katz E.F. (2004). "Office-based buprenorphine treatment for opioid-dependent patients." *Harvard Review of Psychiatry,* 12, (6), 321-338.

Magura, S. and Rosenblum, A. (2001). "Leaving methadone treatment: lessons learned, lessons forgotten, lessons ignored." *Mount Sinai Journal of Medicine,* 68, (1), 62-74.

Manlandro, J. J. Jr. (2005). "Buprenorphine for office-based treatment of patients with opioid addiction." *JAOA: Journal of the American Osteopathic Association,* 105, S8-S13. [online]. Available: http://www.jaoa.org/cgi/content/full/105/6_suppl_3/S8

Methadone 2. (nd). "History of Methadone." [online]. Available: http://www.methadone2.com/history-of-methadone.htm

Mintzer, I. L., Eisenberg, M., Terra, M., MacVane, C., Himmelstein, D. U., Woolhandler, S. (2007). "Treating opioid addiction with buprenorphine-naloxone in community-based primary care settings." *Annals of Family Medicine,* 5, 146-150. [online]. Available: http://www.annfammed.org/cgi/reprint/5/2/146

Moore, B. A., Fiellin, D. A., Barry, D. T., Sullivan, L. E., Chawarski, M. C., O'Conner, P. G., Schottenfield, R. S. (2007) "Primary care office-based buprenorphine treatment: comparison of heroin and prescription opioid dependent patients." *Journal of General Internal Medicine,* 22, (4), 527–530. [online]. Available: http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1829433&blobtype=pdf

Nielsen S., Lee N., Dunlop A., Dietze P., Lintzeris N. and Taylor D. (n.d.). "Benzodiazepine Use in Opioid Substitution Treatment." [online]. Available: http://www.turningpoint.org.au/research/wip/wip_2006/Benzo_use_in_opioid_substitution_treatment.pdf

Opioids.com (nd.a). "A Brief History of Opium." [online]. Available: http://opioids.com/timeline/index.html

Opioids.com (nd.b). "Hidden Pain in a Pill." [online]. Available: http://opioids.com/hydrocodone/vicodin.html

Opioids.com (nd.c). "Plant of Joy." [online]. Available: http://opioids.com/red.html

Rosack, J. (2003). "Buprenorphine efficacy shown in office-based practices*."* Psychiatric News, 38, 2-20. [online]. Available: http://pn.psychiatryonline.org/cgi/content/full/38/19/2

SAMHSA. (2007). "Updated Literature Review." [online]. Available: http://buprenorphine.samhsa.gov/UPDATED_Bup_Lit_Review_Feb_07_rev.pdf

Schifano, F., Corkery, J., Gilvarry, E., Deluca, P., Oyefeso, A. and Ghodse, H. (2005). "Buprenorphine mortality, seizures and prescription data in the UK, 1980-2002." *Human Psychopharmacology: Clinical and Experimental,* 20, 343-348.

Smith, Meredith Y., Bailey, J. Elise, Woody, George E. and Kleber, Herbert D. (2007). "Abuse of buprenorphine in the United States: 2003-2005." *Journal of Addictive Diseases,* 26, (3).

Steentoft, A., B. Teige, P. Holmgren, F. Vuori, J. Kristinsson, A.C. Hansen, G. Ceder, G. Wethe and D. Rollman. (2006). "Fatal poisoning in Nordic drug addicts in 2002." *Forensic Science International,* 160, (1-2), 65-69.

Stein, M. D., Cioe, P., Friedmann P. D. (2005). "Buprenorphine retention in primary care." *Journal of General Internal Medicine,* 20, (11), 1038–1041. [online]. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1490248

Strain E.C., Stoller K., Walsh S.L. and Bigelow G.E. (2000). "Effects of buprenorphine versus buprenorphine/naloxone tablets in non-dependent opioid abusers." [online]. *Psychopharmacology (Berl),* 148, (4), 374-83. Abstract from: PubMed: PMID: 10928310

Sullivan L.E., Chawarski M., O'Connor, P.G., Schottenfeld R.S. and Fiellin D.A. (2005). The practice of office-based buprenorphine treatment of opioid dependence: is it associated with new patients entering into treatment?" *Drug and Alcohol Dependence,* 79, 113-116.

Valenciao M., Emmanuelli J., and Lert F. (2001). "Unsafe injecting practices among attendees of syringe exchange programmes in France." *Addiction,* 96, 597-606.

Vidal-Trecan G., Varescon I., Nabet N. and Bolssonnas. (2003). "Intravenous use of prescribed sublingual buprenorphine tablets by drug users receiving maintenance therapy in France." *Drug and Alcohol Dependence,* 69, 175-181.

Wikipedia. (n.d.). "Buprenorphine." [online]. Available: http://en.wikipedia.org/wiki/Buprenorphine